Zippier Zaps: Faster Electrostatics Calculations

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Macromolecular modeling techniques have contributed enormously to our understanding of macromolecular structures and their relationships to biological function. As computers become more and more powerful, modeling should become a truly predictive science, offering insights into structure-function relationships in systems where a single, static structure is an insufficient description, and providing guidance for the rational design of drugs and engineered macromolecules. For modeling methods to realize their full potential as predictive tools, they must be as accurate as possible.

In this issue, Oberoi and Allewell (1) present a method that offers significant improvements in the speed and accuracy of the treatment of molecular electrostatics, which is currently the largest source of error in the most common quantitative modeling algorithms (energy minimization, molecular dynamics, and Monte Carlo). The independent development of this same approach was recently reported by Holst and Saied (2).

Electrostatic interactions are often modeled with a modified Coulombic approximation. Coulomb's law is the solution to Poisson's equation around a point charge in the case of a homogeneous system with a uniform dielectric constant. This is inappropriate for a macromolecule under physiological conditions, because the macromolecule has a low dielectric constant (~2–4), and it is surrounded by a solution with a high dielectric constant (~80) and containing mobile ions. In this case, the proper mathematical treatment of electrostatic interactions requires the solution of the Poisson-Boltzmann equation (PBE).

The PBE does not have analytical solutions except for very simple geometries, so numerical methods are required. The currently favored approach uses the finite difference method, pioneered by Warwicker and Watson (3) and extended and improved by efforts in many laboratories over the past decade. Finite differences have been applied to both the complete nonlinear form of the PBE and the linearized PBE, a frequently used approximation. (The linearized PBE makes the approximation $sinh(x) = x$, x being the ratio of the electrostatic energy of a unit test charge to the thermal energy,

$$x = e\phi(\mathbf{r})/(kT),$$

where e is the charge on the proton, $\phi(\mathbf{r})$ is the electrostatic potential at point $\mathbf{r}$, k is Boltzmann's constant, and T is the absolute temperature.)

The finite difference method requires a regular cubic grid, which introduces several approximations and their accompanying errors. In particular, the molecular shape must be described by cubic elements, and the charges on each atom must be distributed onto points on the grid. A balance must be struck between the desire for accuracy, which requires a very fine grid, and the burden of computational costs, which rise rapidly with the number of grid points. In typical macromolecular applications, the length of each grid element is about 1 Å.

Oberoi and Allewell (1) describe a major improvement in the efficiency of the finite difference algorithm for solving the nonlinear PBE, using a multigrid approach. Multigridding reduces the computational time very significantly. For example, with a grid of 111^3, the Oberoi and Allewell algorithm was faster by a factor of 10 than optimized successive overrelaxation, generally regarded as a very efficient method. Thus, much finer grids can be used for a given investment of CPU time. And finer grids mean greater accuracy. Earlier this year, Holst and Saied (2) had shown similar results, using the same approach to solve the linearized PBE.

Multigridding accelerates the convergence of numerical solutions to differential equations by working alternatively on a fine grid, where an approximate solution is obtained, and on coarser grids, where the residual equations are solved to high accuracy. The corrections obtained on the coarse grid are interpolated back to the fine grid. The multigrid method gets its efficiency from the fact that the low frequency (long wavelength) part of the error is distributed across the whole system much more rapidly on the coarse grid than it would be when working only on the fine grid. This introduces almost no additional overhead, since calculations on coarse grids are very rapid.

One of the most important results of this research is the demonstration that, the finer the grid, the greater the gain in efficiency given by multigridding. Computational cost grows very slowly with number of grid points, when compared to optimized successive overrelaxation (Fig. 4 of Ref. 1); a fine grid of 181^3 was solved effortlessly when modeling lysozyme, with a resolution of 0.28 Å. Similar observations about efficiency were obtained when multigridding was compared to a variety of other methods (Fig. 4 of Ref. 2).

Oberoi and Allewell have used their new method to carefully examine the predicted pK_a of several residues in lysozyme. When these are calculated for slightly different crystallographic conformations of the protein, the variation in calculated pK_a is often larger than the difference between calculated and experimental pK_a. Similar results were reported earlier, based on variations in electrostatic interactions observed in molecular dynamics simulations (4, 5). These variations, ranging up to 2 pK_a units, suggest that calculations based on a single crystal structure may not always be accurate, and conformational averaging may be needed.

I must admit that initially the remarkable improvement in computational efficiency was somewhat dismaying to me. You and I have just introduced a new method for solving the linearized PBE, based on the finite element approach (6). Finite elements have two main advantages over the finite difference method. First, noncubic elements can be used, offering a more accurate description of molecular surfaces. Second, atomic charges keep their true positions and do not have to be distributed

onto grid points. We have shown that our method is indeed more accurate than the finite difference approach, and we argue that it is nearly competitive from a cost standpoint (6), but speedups of the finite difference algorithm from multigridding obviously attack that argument. Oberoi and Allewell suggest that "a hybrid technique that uses finite elements at the protein boundary and finite difference elsewhere is feasible within the formulation of the multigrid method and may ultimately be the solution of choice, since it would combine the speed of multigrid with the accuracy of finite elements where they are required." This is indeed a very exciting prospect, particularly when considering how to improve the treatment of electrostatics in molecular dynamics and Monte Carlo. Sharp has demonstrated the feasibility of using numerical solutions to the PBE in molecular dynamics (7). Multigridding promises even greater accuracy, using finite differences, finite elements, or the hybrid approach suggested by Oberoi and Allewell.

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